

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant(s): TURSKI, Lechoslaw  
SMITH, Terence

Serial No.: To Be Assigned  
(Continuation Application of PCT/GB99/02112)

Filed: Herewith (December 22, 2000)

For: Treatment of Demyelinating Disorders

Attorney Docket No.: 102286.123

**PRELIMINARY AMENDMENT**

**EXPRESS MAIL LABEL NO.: EL384918288US  
December 22, 2000**

Commissioner of Patents  
Washington, D.C. 20231

**ATTN: BOX PATENT APPLICATION**

Dear Sir:

Prior to the examination of the above-identified application please amend the specification and claims as follows:

**IN THE SPECIFICATION:**

Please amend the specification by inserting before the first line the sentence: "This application is a continuation application of PCT/GB99/02112, filed July 2, 1999, claiming priority to GB 98143380.3 and GB 9824393.4, filed July 2, 1998 and November 6, 1998, respectively, in Great Britain."

Please insert the "Abstract of the Invention" which is attached as a separate page to this Preliminary Amendment.

**IN THE SPECIFICATION**

Please delete the title and insert instead – Treatment of Demyelinating Disorders --.

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IN THE CLAIMS:

REMARKS

Respectfully submitted,

Hollie L. Baker

Date: December 22, 2000

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## CLAIMS

1. (Once Amended) A pharmaceutical composition for treating a demyelinating disorder comprising an inhibitor of the interaction of glutamate with the AMPA receptor complex and of the interaction of glutamate with the kainate receptor complex and a pharmaceutically acceptable carrier.
2. (Once Amended) A pharmaceutical composition for treating a demyelinating disorder comprising an inhibitor of the interaction of glutamate with the AMPA receptor complex and a pharmaceutically acceptable carrier..
3. (Once Amended) A pharmaceutical composition for treating a demyelinating disorder comprising an inhibitor of the interaction of glutamate with the kainate receptor complex and a pharmaceutically acceptable carrier..
4. (Once Amended) The pharmaceutical composition of claim 1, wherein the demyelinating disorder is acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, HIV- or HTLV- myelopathy, progressive multifocal leucoencephalopathy, or a secondary demyelinating disorder.
5. (Once Amended) The pharmaceutical composition of claim 4, wherein the secondary demyelinating disorder is CNS lupus erythematoses, polyarteriitis nodosa, Sjörgren syndrome, sarcoidosis or isolated cerebral vasculitis.
6. (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is an antagonist of the binding of glutamate to the AMPA receptor.
7. (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is an antagonist of the binding of glutamate to the kainate receptor.

8. (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is an L-glutamate derivative, and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate derivative, arylthioxaline, acid amide, hydrazone, quinoline, quinolinone, quinoxaline, quinoxalinedione, triazoloquinoxalinedione, pyrrolylquinoxalindione, quinazolinone, quinazolinedione, quinoxalinone, phenylpyridazinoindole-dione, indenopyrazinone, imidazoloquinoxalinone, indolopyrazinone, imidazo-pyrazinone, triazolo-pyrazinone, benzothiadiazine, 4-hydroxypyrrolone, pyrrolo-pyridazinone, phthalazine, quinolone, amino-alkanoic acid, isatine, phenyl-azolophthalazine, amino- or desamino-2,3-benzodiazepine,  $\beta$ -carboline-3-carboxylic acid, alkoxy-phenyl-benzodiazepine, isoquinolinyl-carboxylic acid derivatives, acetyl-aminophenyl-dihydro-methyl-dioxolo-benzodiazepine, pyrimidinone, oxadiazole, isatinoxime, decahydroisoquinoline, piperazine derivative, tetramic acid derivatives, or a sulphonamide.

9. (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is L-glutamic acid diethyl ester, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX), 6,7-dinitro-quinoxaline-2,3-dione (DNQX), 6-nitro-7-cyano-quinoxaline-2,3-dione (CNQX), 6-(1-imidazolyl)-7-nitro-quinoxaline-2,3(1H,4H)-dione (YM90K), (3RS,4aRS,6RS,8aRS)-6-)-2-(1H-tetrazole-5-yl)ethyl)-decahydroiso-quinoline-3-carboxylic acid (LY293558), 9-methyl-amino-6-nitro-hexahydro-benzo(F) quinoxalinedione (PNQX), 8-methyl-5-(4-(N,N-dimethylsulphonamoyl)phenyl)-6,7,8,9-tetrahydro-1H-pyrrolo[3,2h]-isoquinoline-2,3-dione-3-O-(3-hydroxybutyric acid 2-yl)oxime (NS 1209), 6,7-dichloro-2-(1H)-quinolinone-3-phosphonate (S 17625-2), and [1,2,3,4-tetrahydro-7-morpholinyl-2,3-dioxo-6-(trifluoromethyl)quinoxaline-1-yl]methyl-phosphonate (ZK200775), 1-(4-aminophenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine (GYK152466), (-)-1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-methylcarbamoyl-2,3-benzodiazepine (GYK153773), topiramate, 3-(2-chlorophenyl)-2-[2-[6-[(diethylamino)methyl]-2-pyridinyl]ethenyl]-6-fluoro-4(3H)-quinazolinone (CP465022) and 5-(2-[N,N-dimethylamino]oxy-phenyl)-3-phenyl-1,2,4-oxadiazole (BIIR561).

10. (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is an AMPA receptor channel blocker.

11. (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is a kainate receptor channel blocker.

5 12. (Once Amended) The pharmaceutical composition of claim 10, wherein the AMPA receptor channel blocker is fluorowillardiine or Joro spider toxin.

13. (Once Amended) The pharmaceutical composition of claim 11, wherein the kainate receptor channel blocker is fluorowillardiine or Joro spider toxin.

10 14. (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is combined with one or more of: an immunosuppressive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody  
15 against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1), a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs), or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).

15. Cancelled.

20 16. Cancelled.

17. Cancelled.

18. A method of treating a demyelinating disorder comprising administering an effective amount of an inhibitor of the interaction of glutamate with the AMPA receptor complex and of the interaction of glutamate with the kainate receptor complex.  
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19. A method of treating a demyelinating disorder comprising administering a combination of an effective amount of an inhibitor of the interaction of glutamate

with the AMPA receptor complex and of the interaction of glutamate with the kainate receptor complex with combined with one or more of: an immunosuppressive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1), a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs), or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).

20. The method of claim 19, wherein said combination is administered simultaneously, separately, or sequentially.

## COMPARE COPY OF AMENDED AND ADDED CLAIMS

1. The use of ~~(Once Amended)~~ **A pharmaceutical composition for treating a demyelinating disorder comprising** an inhibitor of the interaction of glutamate with the AMPA receptor complex and of the interaction of glutamate with the kainate receptor complex in the manufacture of a medicament **and a pharmaceutically acceptable carrier.**

2. The use of ~~(Once Amended)~~ **A pharmaceutical composition** for treating a demyelinating disorder **comprising** an inhibitor of the interaction of glutamate with the AMPA receptor complex in the manufacture of a medicament **and a pharmaceutically acceptable carrier.**

3. The use of ~~(Once Amended)~~ **A pharmaceutical composition** for treating a demyelinating disorder **comprising** an inhibitor of the interaction of glutamate with the kainate receptor complex in the manufacture of a medicament for treating a demyelinating disorder. **and a pharmaceutically acceptable carrier.**

4. The use according to any preceding claim ~~(Once Amended)~~ **The pharmaceutical composition of claim 1**, wherein the demyelinating disorder is acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, HIV- or HTLV-myelopathy, progressive multifocal leucoencephalopathy, or a secondary demyelinating disorder.

5. The use according to any of claims 1 to 3 ~~(Once Amended)~~ **The pharmaceutical composition of claim 4**, wherein the secondary demyelinating disorder is CNS lupus erythematosus, polyarteritis nodosa, Sjögren syndrome, sarcoidosis or isolated cerebral vasculitis.



6. The use according to any of claims 1 to 5 (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is an antagonist of the binding of glutamate to the AMPA receptor.

7. The use according to any of claim 1 to 5 (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is an antagonist of the binding of glutamate to the kainate receptor.

8. The use according to any preceding claim (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is an L-glutamate derivative, and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate derivative, arylthioxaline(42), acid amide(59), hydrazone(48), quinoline(51), quinolinone(70,78), quinoxaline(8,9,13,14,15,17,20,47,50,52,53,54,55,56), quinoxalinedione(7,11,23,43,57,58,60,61,74,77,81), triazoloquinoxalinedione(3,4,5), pyrrolylquinoxalindione(6), quinazolinone(22), quinazolinedione(35), quinoxalinone(29), phenylpyridazinoindoledione(41), indenopyrazinone(24,32,63,65,66,67,68), imidazoloquinoxalinone(12), indolo-pyrazinone(64), imidazo-pyrazinone(31,33,34,37,44,62), triazolo-pyrazinone(30), benzothiadiazine(16,36), 4-hydroxypyrrolone, pyrrolo-pyridazinone(40), phthalazine(25), quinolone(18,19), amino-alkanoic acid(1), isatine(72), phenyl-azolophthalazine, amino- or desamino-2,3-benzodiazepine(71),  $\beta$ -carboline-3-carboxylic acid, alkoxy-phenyl-benzodiazepine, isoquinoliny-carboxylic acid derivatives(75), acetyl-aminophenyl-dihydro-methyl-dioxolo-benzodiazepine, pyrimidinon(46), oxadiazol(80), isatinoxime, decahydroisoquinoline(69,73,76), piperazine derivative(2), tetramic acid derivatives(39), or a sulphamate. (The reference numbers used above correspond with the numbers used in the list of antagonists provided in the description.)

9. The use according to any of claims 1 to 7 (Once Amended) The pharmaceutical composition of claim 1, wherein the inhibitor is L-glutamic acid diethylester, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX), 6,7-dinitro-quinoxaline-2,3-dione (DNQX), 6-nitro-7-cyano-quinoxaline-2,3-dione (CNQX), 6-(1-imidazolyl)-7-nitro-quinoxaline-2,3(1H,4H)-dione (YM90K),

(3RS,4aRS,6RS,8aRS)-6-(1H-tetrazole-5-yl)ethyl)-decahydroiso-quinoline-3-carboxylic acid (LY293558), 9-methyl-amino-6-nitro-hexahydro-benzo(F)quinoxalinedione (PNQX), 8-methyl-5-(4-(N,N-dimethylsulphamoyl)phenyl)-6,7,8,9-tetrahydro-1H-pyrrolo[3,2h]-isoquinoline-2,3-dione-3-O-(3-hydroxybutric acid 2-yl)oxime (NS 1209), 6,7-dichloro-2-(1H)-quinolinone-3-phosphonate (S 17625-2), and [1,2,3,4-tetrahydro-7-morpholinyl-2,3-dioxo-6-(trifluoromethyl)quinoxaline-1-yl]methyl-phosphonate (ZK200775), 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYK152466), (-)-1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-methylcarbamoyl-2,3-benzodiazepine (GYK153773), topiramate, 3-(2-chlorophenyl)-2-[2-[6-[(diethylamino)methyl]-2-pyridinyl]ethenyl]-6-fluoro-4(3H)-quinazolinone (CP465022) and 5-(2-[N,N-dimethylamino]oxy-phenyl)-3-phenyl-1,2,4-oxadiazol (BIIR561).

10. ~~The use according to any of claims 1 to 5~~**(Once Amended) The pharmaceutical composition of claim 1**, wherein the inhibitor is an AMPA receptor channel blocker.

11. ~~The use according to any of claims 1 to 5~~**(Once Amended) The pharmaceutical composition of claim 1**, wherein the inhibitor is a kainate receptor channel blocker.

12. ~~The use according to~~**(Once Amended) The pharmaceutical composition of** claim 10, wherein the AMPA receptor channel blocker is fluorowillardiine or Joro spider toxin.

13. ~~The use according to~~**(Once Amended) The pharmaceutical composition of** claim 11, wherein the kainate receptor channel blocker is fluorowillardiine or Joro spider toxin.

14. ~~The use according to any preceding claim~~**(Once Amended) The pharmaceutical composition of claim 1**, wherein the inhibitor is combined with one or more of: an immunosuppressive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-

alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1), a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs), or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).

15. ~~A pharmaceutical composition comprising an inhibitor as described in any of claims 1 to 14 and a pharmaceutically acceptable carrier.~~ **Cancelled.**

16. ~~A combined preparation of an inhibitor as described in any claims 1 to 14 and~~  
**Cancelled.**

17. ~~The invention substantially as hereinbefore described~~ **Cancelled.**

**18. A method of treating a demyelinating disorder comprising administering an effective amount of an inhibitor of the interaction of glutamate with the AMPA receptor complex and of the interaction of glutamate with the kainate receptor complex.**

**19. A method of treating a demyelinating disorder comprising administering a combination of an effective amount of an inhibitor of the interaction of glutamate with the AMPA receptor complex and of the interaction of glutamate with the kainate receptor complex with combined with one or more of: an immunosuppressive agent (e.g. corticotrophin, a glucocorticoid, cyclophosphamide, cyclosporine, azothioprine or mitozantrone), an interferon (IFN; IFN-beta-1a e.g. Rebif and Avonex; IFN-beta-1b e.g. Betaseron and Betaferon; IFN-alpha-2a e.g. Alphaferone; IFN-alpha-2b e.g. Viraferon), a phosphodiesterase type IV inhibitor, a humanised monoclonal antibody against a leukocyte adhesion molecule (e.g. Antegran), a synthetic polypeptide (e.g. glatiramer acetate, copolymer-1), a tissue matrix metalloproteinase (MMP) inhibitor (e.g. hydroxamic acid-based inhibitors of MMPs), or a tumour necrosis factor (TNF) inhibitor (e.g. Thalidomide or TNF-receptor immunoglobulin fusion protein).**

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Additions appear as **Bold-Underline** text